


FORM PTO-1390 (REV 11-98)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 146.1375
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371.			U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/018073
INTERNATIONAL APPLICATION NO. PCT/FR00/01568	INTERNATIONAL FILING DATE June 8, 2000	PRIORITY DATE CLAIMED June 9, 1999	
TITLE OF INVENTION NEW DERIVATIVES OF ECHINOCANDINE, THEIR PREPARATION PROCESS AND THEIR USE AS ANTIFUNGALS			
APPLICANT(S) FOR DO/EO/US FAIVEAU et al			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input checked="" type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 			
Items 11. to 16. below concern document(s) or information included:			
<ol style="list-style-type: none"> 11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information: French International Preliminary Examination Report; PCT/IB/306 			

U.S. APPLICATION NO. (if known, see 37 CFR 1.51) 10/018073		INTERNATIONAL APPLICATION NO. PCT/FR00/01568		ATTORNEY'S DOCKET NUMBER 146.1375	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. \$970.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$840.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$760.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$670.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$96.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY \$1040.00 \$1040.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
<input type="checkbox"/> CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	18 - 20 =	0	X \$18.00	\$ 1040.00	
Independent claims	1 - 3 =	0	X \$78.00	\$	
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$260.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$ 1040.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$ 1040.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$ 1040.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED =				\$ 1040.00	
				Amount to be:	\$
				refunded	
				charged	\$
a. <input checked="" type="checkbox"/> <u>PTO Form 2038 is enclosed.</u> A check in the amount of \$_____ to cover the above fees is enclosed.					
b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed.					
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-2275</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Bierman, Muserlian and Lucas 600 Third Avenue New York, NY 10016					
				 SIGNATURE:	
				Charles A. Muserlian NAME	
				19,683 REGISTRATION NUMBER	

Our Ref.: 146.1375

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :
FAUVEAU et al :
PCT/FR00/01568 : PCT Date: June 8, 2000
Serial No.: :
Filed: Concurrently Herewith :
For: NEW DERIVATIVES...AS ANTI- :
FUNGALS :
600 Third Avenue
New York, NY 10016
December 4, 2001

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

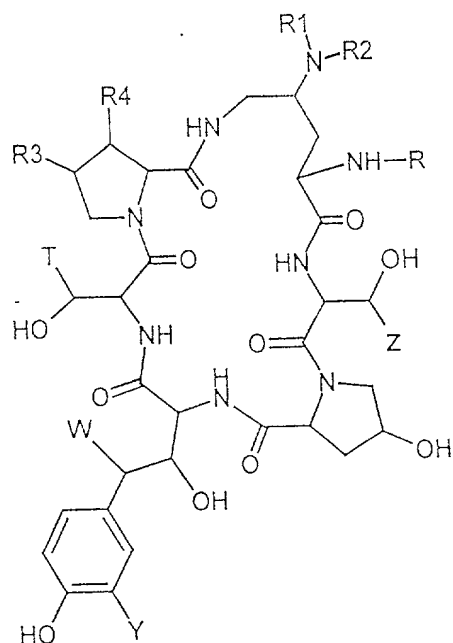
IN THE SPECIFICATION:

Page 1, before line 1, insert

--This is a 371 of PCT/FR00/01568 filed on June 8, 2000.--

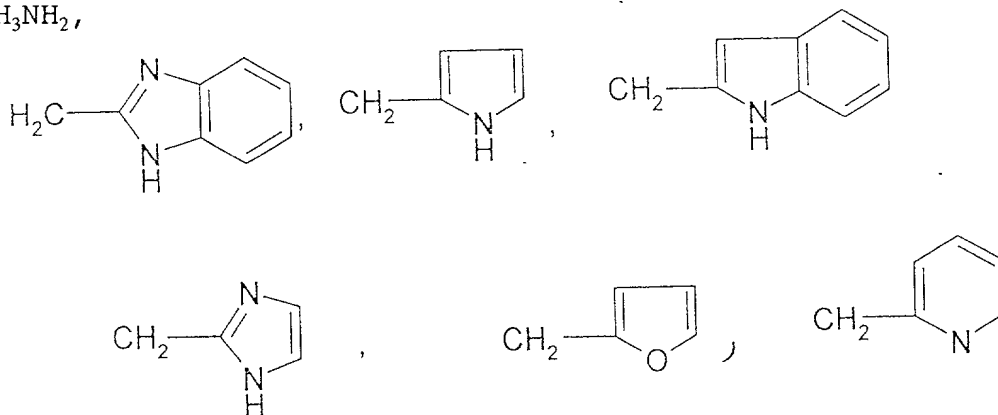
IN THE CLAIMS:

Claim 1 (amended) A compound selected from the group
consisting of all possible isomeric forms and their mixtures, a
compound of the formula



(I)

either R_1 is hydrogen or methyl and R_2 is selected from the group consisting of cyclohexyl substituted by an amine, $\text{CH}_2\text{CH}_2\text{NHCH}_3$, $\text{CH}_2\text{CHCH}_3\text{NH}_2$,



$\text{CHCH}_3\text{CH}_2\text{NH}_2$, $-(\text{CH}_2)_a\text{OH}$ where a is an integer of 1 to 8, $(\text{CH}_2)_b\text{-C}\equiv\text{N}$ where

b is an integer of 1 to 8, $\text{CHCH}_3\text{C}_6\text{H}_5$, $(\text{CH}_2)_2\text{-C}(\text{CH}_3)_2\text{NHCOCF}_3$, and $\text{CHCH}_3(\text{CH}_2)_d\text{OH}$ where d is an integer of 1 to 8

or R_1 and R_2 together with the nitrogen to which they are attached

form a ring of 3, 4 or 5 carbons optionally substituted by an amine
R₃ is selected from the group consisting of hydrogen, methyl and
hydroxyl

R₄ is hydrogen or hydroxyl,

R is selected from the group consisting of alkyl and cycloalkyl of
up to 30 carbon atoms, optionally containing at least one
heteroatom, at least one heterocycle and alkyl or cyclic acyl of up
to 30 carbon atoms optionally containing at least one heteroatom,
and/or at least one heterocycle,

T is selected from the group consisting of hydrogen, methyl,
-CH₂CONH₂, -CH₂C=N, -(CH₂)₂NH₂ and -(CH₂)₂Nalk⁺X⁻, X is halogen and alk
is alkyl of up to 8 carbon atoms,

Y is selected from the group consisting of hydrogen, hydroxyl,
halogen and -OSO₃H or the salt thereof,

W is hydrogen or OH,

Z is hydrogen or methyl and its non-toxic, pharmaceutically
acceptable acid addition salt.

Claim 2 (amended) A compound of claim 1 in which T is
hydrogen.

Claim 3 (amended) A compound of claim 1 in which W is
hydrogen.

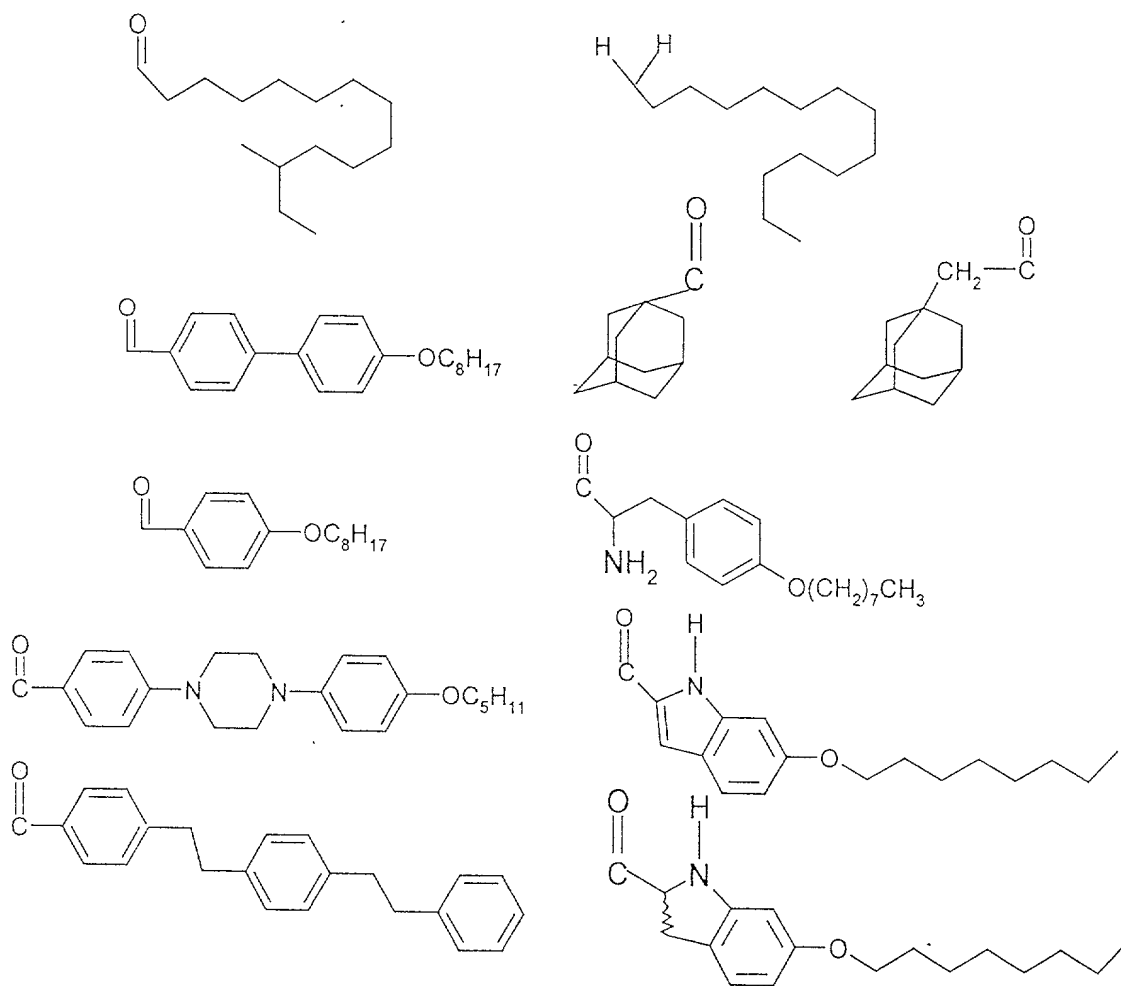
Claim 4 (amended) A compound of claim 1 in which Z is
methyl.

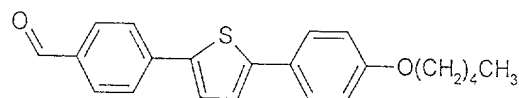
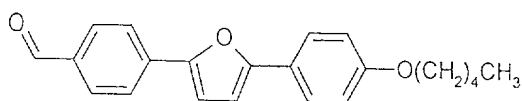
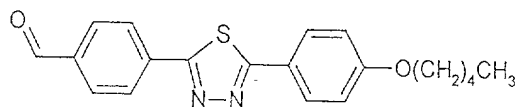
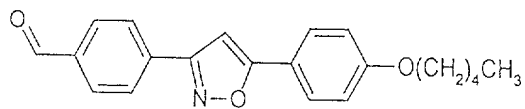
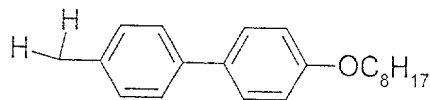
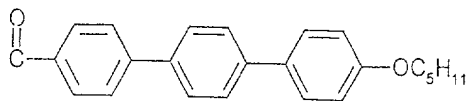
Claim 5 (amended) A compound of claim 1 in which Y is hydrogen.

Claim 6 (amended) A compound of claim 1 in which R₃ is methyl.

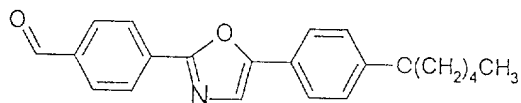
Claim 7 (amended) A compound of claim 1 in which R₄ is hydroxyl.

Claim 8 (amended) A compound of claim 1 in which R is selected from the group consisting of

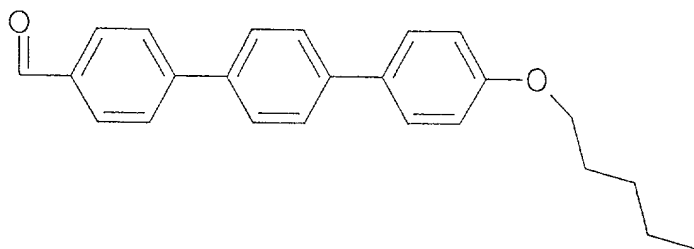




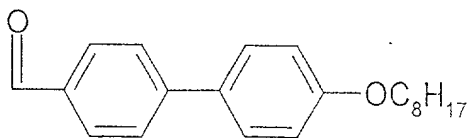
and



Claim 9 (amended) A compound of claim 8 in which R is

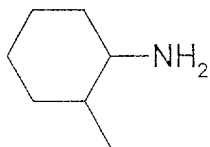


Claim 10 (amended) A compound of claim 8 in which R is

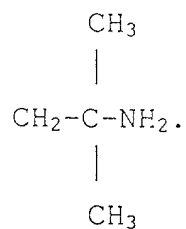


Claim 11 (amended) A compound of claim 1 in which R₁ is hydrogen.

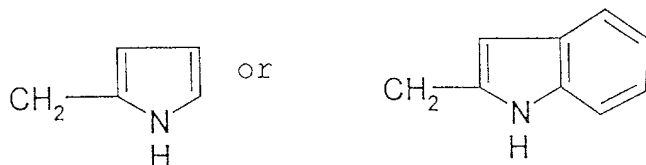
Claim 12 (amended) A compound of claim 1 in which R₂ is



Claim 13 A compound of claim 1 in which R₂ is selected from the group consisting of



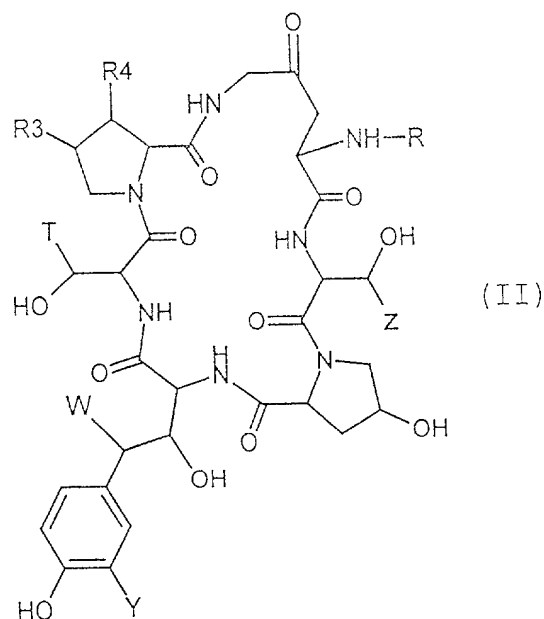
Claim 14 (amended) A compound of claim 1 in which R2 is



Claim 15 (amended) A compound of claim 1 selected from the group consisting of

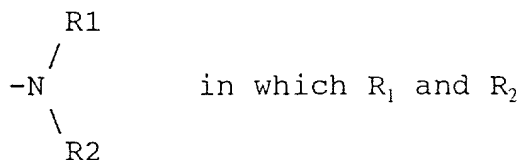
- 1-[4-[[(1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer B), and
- trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

Claim 16 (amended) A process for the preparation of a compound of claim 1 comprising reacting a compound of the formula



(II)

wherein R, R₃, R₄, T, Y, W and Z are defined as in claim 1 with an amine or amine derivative capable of introducing



are defined as in claim 1 and optionally to the action of a reducing agent

and/or an amine functionalization agent,

and/or an acid to form the salt of the product of claim 1,

and/or a separation agent of the different isomers obtained.

Cancel claims 17 and 18 and add the following claims.


--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS


Charles A. Muserlian, #19,683
Attorney for Applicant(s)
Tel. # (212) 661-8000

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Enclosure: Return Receipt Postcard


--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS


Charles A. Muserlian, #19,683
Attorney for Applicant(s)
Tel. # (212) 661-8000

CAM:sd

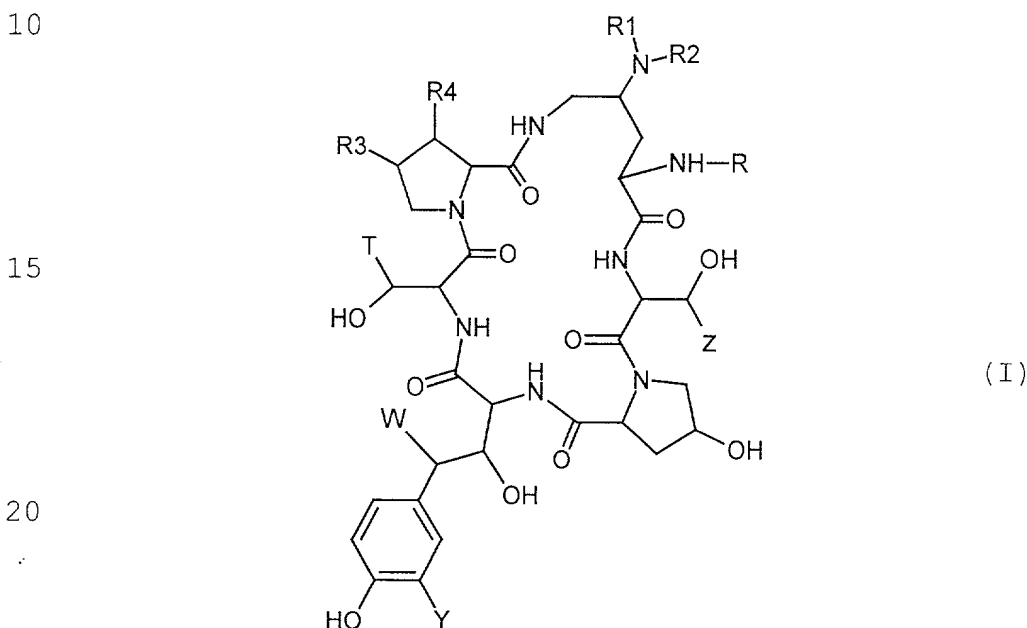
Enclosures: Marked-Up Version of Specification and Claims
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New derivatives of echinocandine, their preparation process
and their use as antifungals.

-- This is a 371 of PCT/FR00/01568 filed June 8, 2000.--

The present invention relates to new derivatives of
 5 echinocandine, their preparation process and their use as
 antifungals.

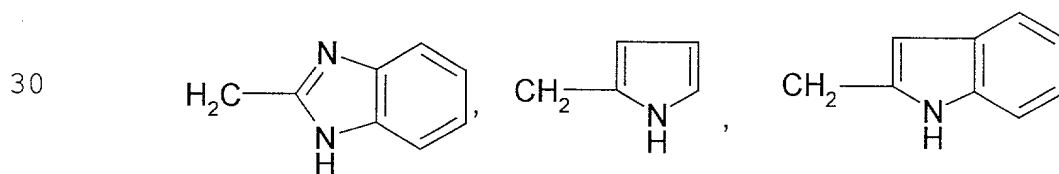
A subject of the invention is, in all possible isomer
 forms as well as their mixtures, the compounds of formula
 (I):



in which

25 either R_1 represents a hydrogen atom or a methyl radical.

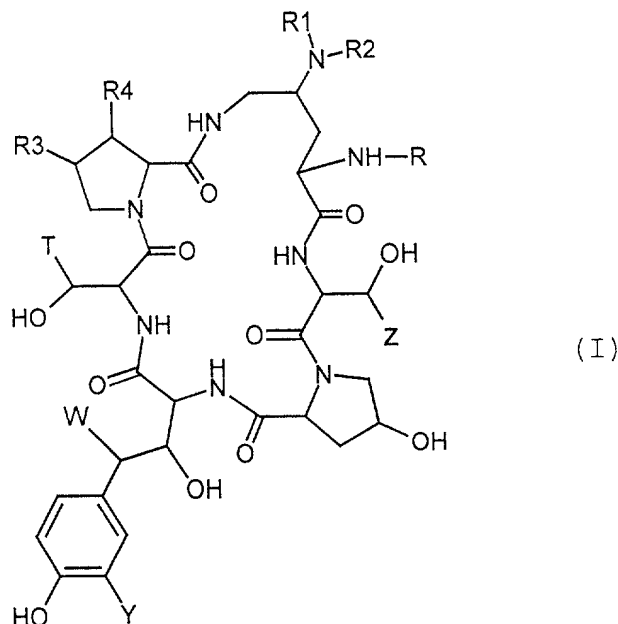
R_2 represents a cyclohexyl radical substituted by an amine, a
 $\text{CH}_2\text{CH}_2\text{NHCH}_3$ radical, a $\text{CH}_2\text{CHCH}_3\text{NH}_2$ radical, a



radical, a $\text{CHCH}_3\text{CH}_2\text{NH}_2$ radical, a $-(\text{CH}_2)_a\text{OH}$ radical, a

A compound selected from the group consisting of

- 1) ~~the~~ ^{and} all possible isomeric forms as well as their mixtures, ~~the~~ ^{the} compounds of formula (I):

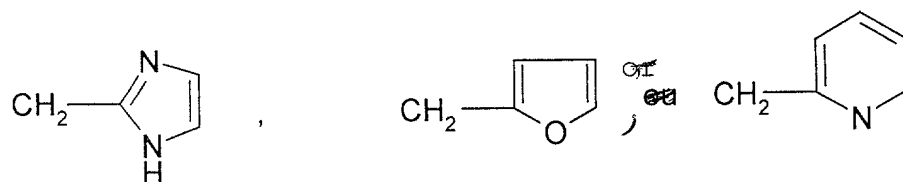
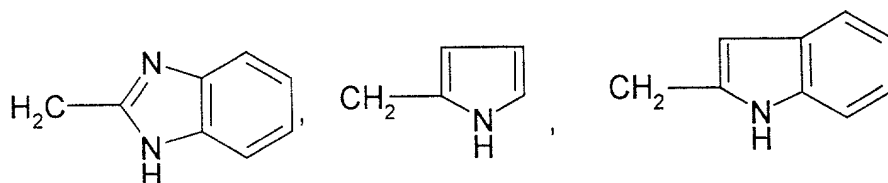


in which

- 20 ~~either~~ ^{is} ~~R₁ represents a hydrogen atom or a methyl radical.~~ ^{and}

~~R₂ represents a cyclohexyl radical substituted by an amine, a CH₂CH₂NHCH₃ radical, a CH₂CHCH₃NH₂ radical, a~~

is selected from the group consisting of



~~radical, a CHCH₃CH₂NH₂ radical, a -(CH₂)_aOH radical, a~~ ^{where}

- 35 ~~representing an integer comprised between 1 and 8, a (CH₂)_b-C≡N radical~~ ^{where}

~~b representing an integer comprised between 1 and 8, a CHCH₃C₆H₅ radical, a (CH₂)-C(CH₃)₂NHCOCF₃ radical, and~~

CHCH₃(CH₂)^{where}dOH ~~radical~~, d ^{is} representing an integer comprised ^{of} between 1 ^{to} and 8

or R₁ and R₂ together with the nitrogen ^{to which they are attached} which carries them form a ring ^{of} with 3, 4 or 5 carbons optionally substituted by

5 an amine

R₃ ~~represents a hydrogen atom, a methyl or hydroxyl radical~~

R₄ ~~represents a hydrogen atom or a hydroxyl radical~~

R ~~represents a linear or branched or cyclic chain containing~~

up to 30 carbon atoms, optionally containing ^{at least} one or more heteroatoms, ^{at least} one or more heterocycles, ^{and alkyl} or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms optionally containing ^{at least} one or more heteroatoms and/or ^{at least} one or more heterocycles,

T ~~represents a hydrogen atom, a methyl radical, a -CH₂CONH₂, -CH₂C≡N radical, a -(CH₂)₂NH₂ or -(CH₂)₂Nalk¹⁵X¹⁵ radical, X being a halogen atom and alk¹⁵, an alkyl radical containing up to 8 carbon atoms,~~

Y ~~represents a hydrogen atom, a hydroxyl radical or a halogen atom or an -OSO₃H radical or one of the salts of this radical,~~

20 W ~~represents a hydrogen atom or an OH radical,~~

Z ~~represents a hydrogen atom or a methyl radical,~~

^{pharmaceutically acceptable acid} as well as the addition salts with acids of the products of formula (I).

2) ~~The compounds of formula (I) defined in claim 1 in which~~

25 T ~~represents a hydrogen atom.~~

3) ~~The compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.~~

4) ~~The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.~~

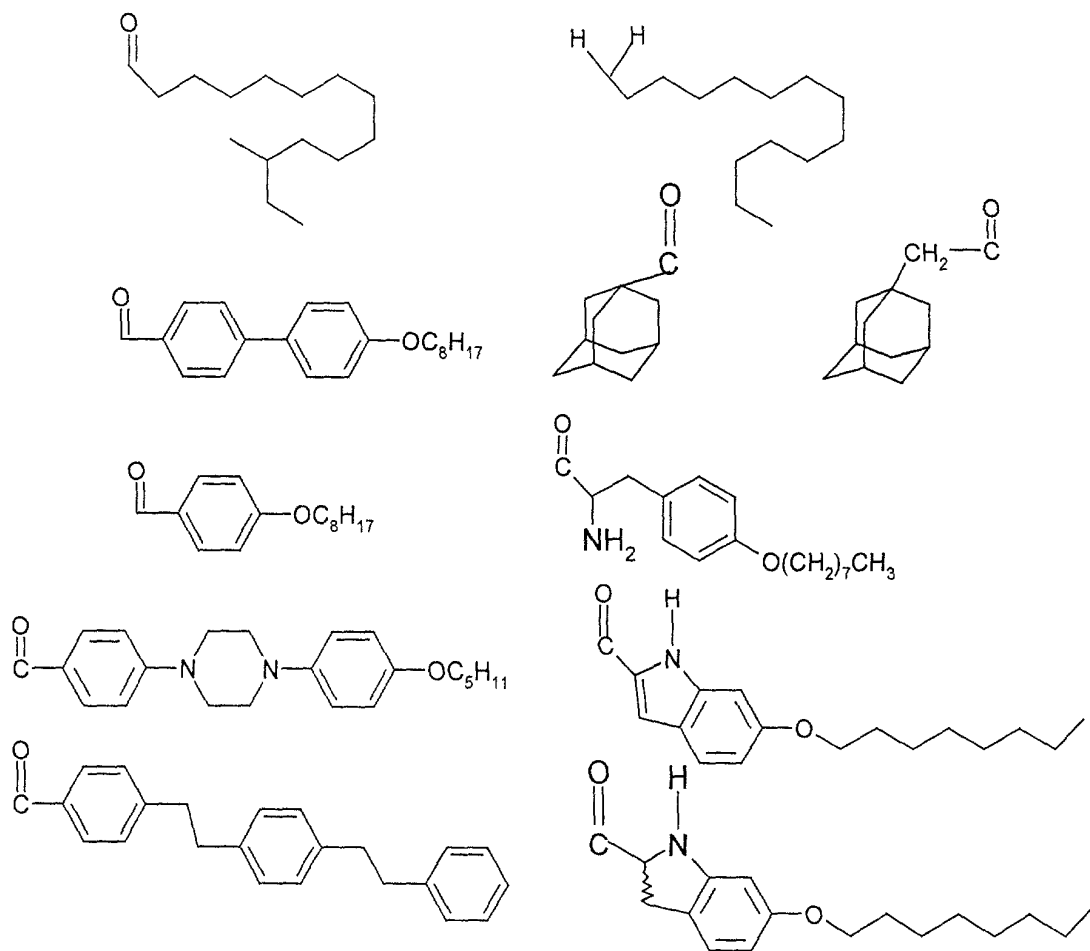
30 5) ~~The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.~~

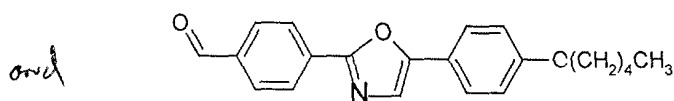
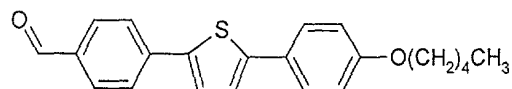
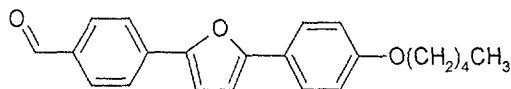
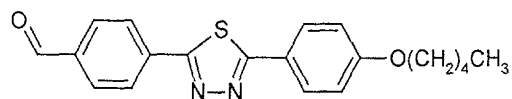
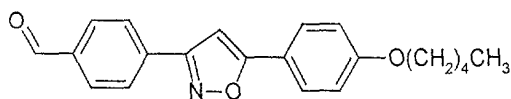
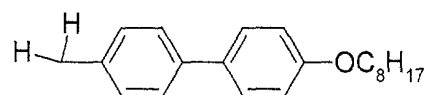
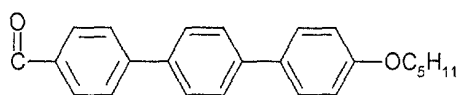
6) ~~The compounds of formula (I) defined in any one of claims 1 to 5 in which R₃ represents a methyl radical.~~

7) ~~The compounds of formula defined in any one of claims 1 to 6 in which R₄ represents a hydroxyl radical.~~

FOOTNOTES

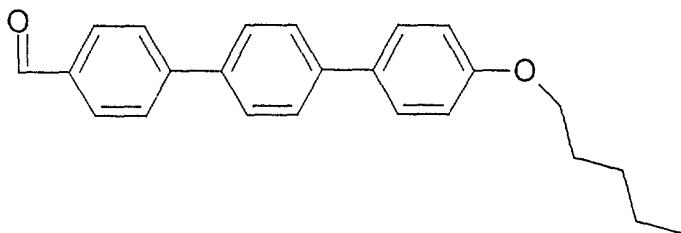
5





radical.

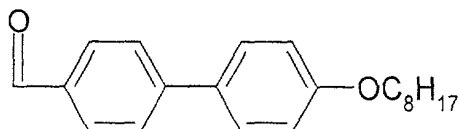
- 9) ^AThe compounds of formula (I) defined in claim 8, in which R ^{is} ~~represents a~~



10

~~chain.~~

- 10) ^AThe compounds of formula (I) defined in claim 8, in which R ^{is} ~~represents a~~

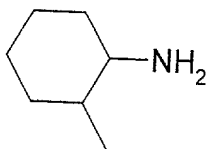


20

~~chain.~~

- 11) ^AThe compounds of formula (I) defined in any one of claims 1 to 10 in which R₁ is ^{hydrogen} ~~a hydrogen atom.~~

12) ^A ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is~~

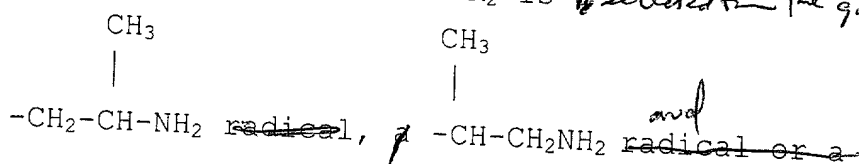


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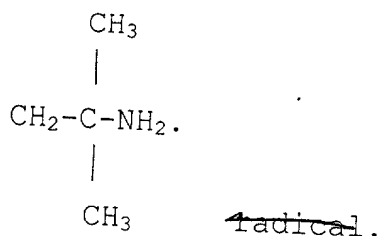
~~radical.~~

13) ^A ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is~~

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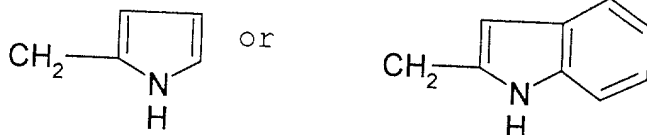
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14) ^A ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is~~

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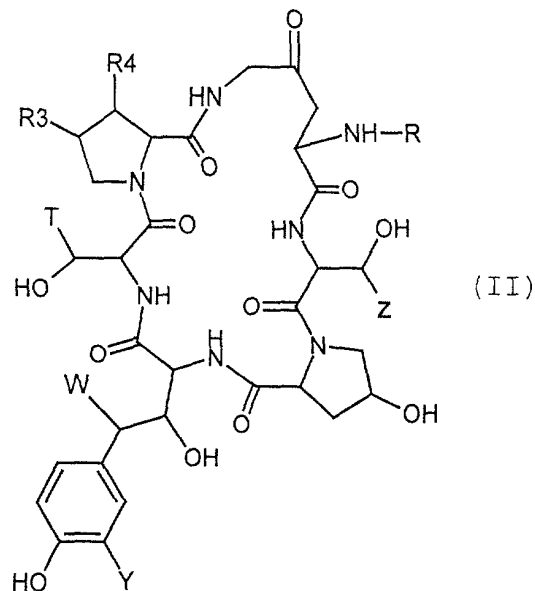


~~radical.~~

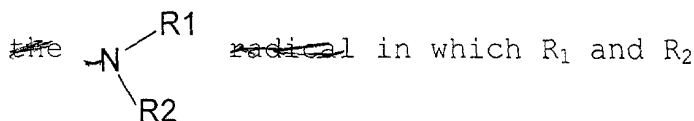
15) ^B ~~The compounds of formula (I) defined in any one of claims 1 to 14 the names of which follow:~~

- 1-[4-[[[(1H-benzimidazol-2-yl)-methyl]-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B), and
- 35 - trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

16) ~~a~~ ^a Process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15 ~~comprising reacting a~~ characterized in that a compound of ^{the} formula (II)



wherein ^{are defined as in claim 1} in which R, R₃, R₄, T, Y, W and Z ~~retain their previous~~ ^{with} meaning, is subjected to the action of an amine or amine derivative capable of introducing



^{are defined as in claim 1} ~~retain their previous meaning and if desired~~ ^{optionally} to the action of a reducing agent and/or an amine functionalization agent, and/or an acid ~~in order~~ to form the salt of the product ^{of claim 1} obtained,

and/or a separation agent of the different isomers obtained, ~~and the sought compound of formula (I) is thus obtained.~~

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

18) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.

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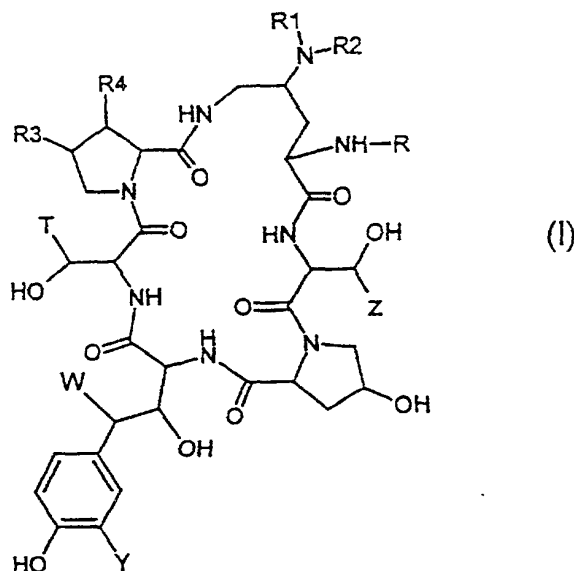
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[Suite sur la page suivante]

(54) Title: ECHINOCANDIN DERIVATIVES, METHOD FOR PREPARING SAME AND APPLICATION AS ANTIFUNGAL AGENTS

(54) Titre: NOUVEAUX DERIVES DE L'ECHINOCANDINE, LEUR PROCEDE DE PREPARATION ET LEUR APPLICATION COMME ANTIFONGIQUES



(57) Abstract: The invention concerns in all possible isomeric forms as well as their mixtures, compounds of formula (I) wherein: either R₁ represents H or CH₃ and R₂ represents cyclohexyl substituted by an amine, a (CH₂)_b-C≡N radical; or R₁ and R₂ form with the nitrogen which bears them a cycle with 3, 4 or 5 carbons optionally substituted by an amine; R₃ represents hydrogen, methyl or hydroxyl; R₄ represents hydrogen or hydroxyl; R represents a linear, branched or cyclic chain; T represents hydrogen, methyl, CH₂CONH₂.

[Suite sur la page suivante]

FOOTER "E208FOOT"

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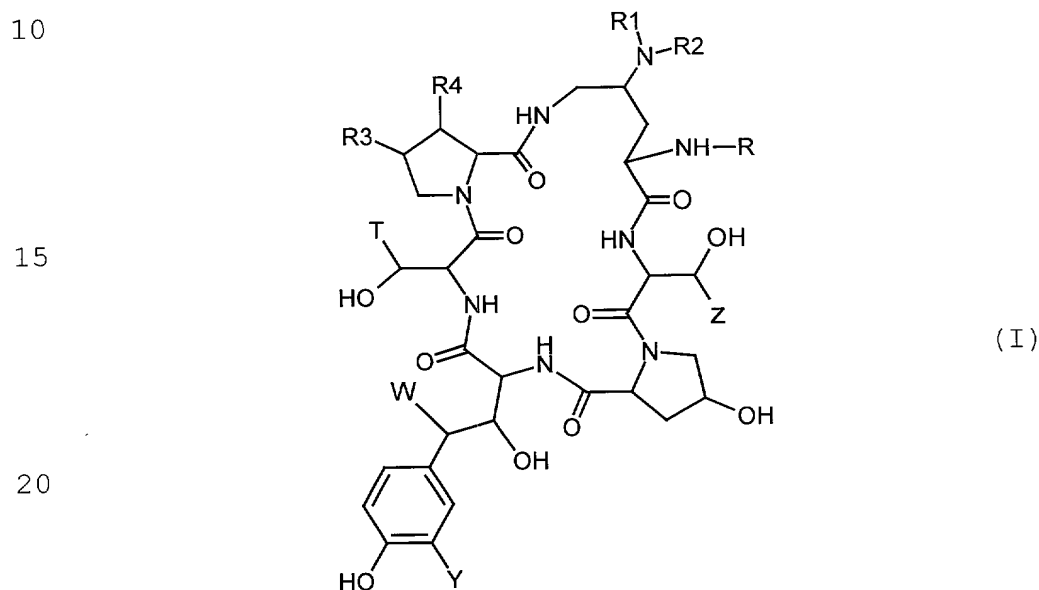
$\text{CH}_2\text{C}\equiv\text{N}$, a $(\text{CH}_2)_2\text{NH}_2$ or $(\text{CH}_2)_2\text{Nalk}^+\text{X}^-$ radical, X being halogen and alk an alkyl radical; Y represents hydrogen, hydroxyl, halogen or OSO_3H ; W represents H or OH; Z represents H, CH_3 . The compounds of formula (I) have antifungal properties.

(57) Abrégé: L'invention a pour objet sous toutes les formes d'isomères possibles ainsi que leurs mélanges, les composés de formule (I) dans lesquels ou bien R_1 : H ou CH_3 et R_2 cyclohexyle substitué par une amine, un radical $(\text{CH}_2)_b\text{C}\equiv\text{N}$ ou bien R_1 et R_2 forment avec l'azote qui les porte un cycle à 3, 4 ou 5 carbones éventuellement substitué par une amine, R_3 hydrogène, méthyle ou hydroxyle, R_4 hydrogène ou hydroxyle, R représente une chaîne linéaire, ramifiée ou cyclique, T hydrogène, méthyle, CH_2CONH_2 , $\text{CH}_2\text{C}\equiv\text{N}$, un radical $(\text{CH}_2)_2\text{NH}_2$ ou $(\text{CH}_2)_2\text{Nalc}^+\text{X}^-$, X halogène et alc alkyle, Y hydrogène, hydroxyle, halogène ou OSO_3H , W H ou OH, Z H, CH_3 . Les composés de formule (I) présentent des propriétés antifongiques.

New derivatives of echinocandine, their preparation process
and their use as antifungals.

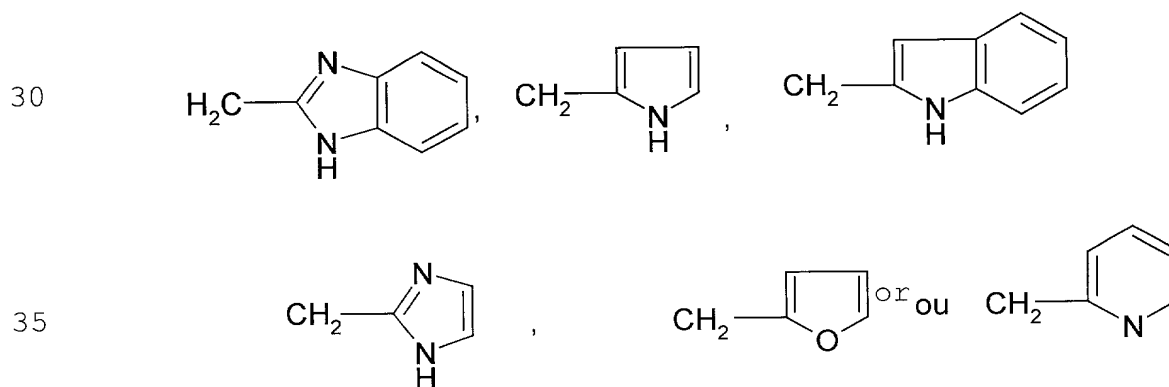
The present invention relates to new derivatives of
5 echinocandine, their preparation process and their use as
antifungals.

A subject of the invention is, in all possible isomer
forms as well as their mixtures, the compounds of formula
(I):



in which

25 either R₁ represents a hydrogen atom or a methyl radical.
R₂ represents a cyclohexyl radical substituted by an amine, a
CH₂CH₂NHCH₃ radical, a CH₂CHCH₃NH₂ radical, a



radical, a CHCH₃CH₂NH₂ radical, a -(CH₂)_aOH radical, a

representing an integer comprised between 1 and 8, a $(\text{CH}_2)_b\text{-C}\equiv\text{N}$ radical, b representing an integer comprised between 1 and 8, a $\text{CHCH}_3\text{C}_6\text{H}_5$ radical, a $(\text{CH}_2)\text{-C}(\text{CH}_3)_2\text{NHCOCF}_3$ radical, a $\text{CHCH}_3(\text{CH}_2)_d\text{OH}$ radical, d representing an integer comprised

5 between 1 and 8

or R_1 and R_2 form together with the nitrogen which carries them a ring with 3, 4 or 5 carbons optionally substituted by an amine

R_3 represents a hydrogen atom, a methyl or hydroxyl radical

10 R_4 represents a hydrogen atom or a hydroxyl radical

R represents a linear or branched or cyclic chain containing up to 30 carbon atoms, optionally containing one or more heteroatoms, one or more heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms

15 optionally containing one or more heteroatoms and/or one or more heterocycles,

T represents a hydrogen atom, a methyl radical, a CH_2CONH_2 radical, $\text{CH}_2\text{C}\equiv\text{N}$, a $(\text{CH}_2)_2\text{NH}_2$ or $(\text{CH}_2)_2\text{Nalk}^+\text{X}^-$ radical, X being a halogen atom and alk an alkyl radical containing up to 8

20 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO_3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical,

25 as well as the addition salts with acids of the products of formula (I).

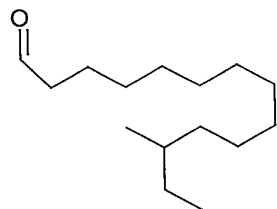
Among the addition salts with acids, there can be mentioned those formed with mineral acids, such as hydrochloric, hydrobromic, sulphuric or phosphoric acid or
30 with organic acids such as formic, acetic, trifluoroacetic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic and aspartic acids, alkanesulphonic acids, such as methane or ethane sulphonic acid, arylsulphonic acids such as benzene or paratoluene sulphonic
35 acids.

Among the preferred compounds of the invention, there can quite particularly be mentioned the compounds of formula I in which T represents a hydrogen atom, those in which W

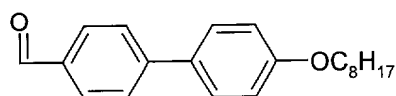
represents a hydrogen atom, those in which Z represents a methyl radical, those in which Y represents a hydrogen atom, those in which R_3 represents a methyl radical, those in which R_4 represents a hydroxyl radical, and those in which R

5 represents a

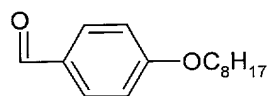
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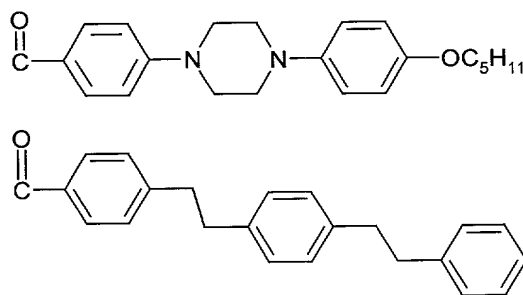
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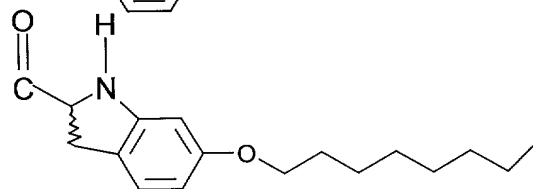
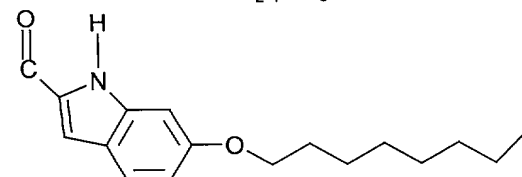
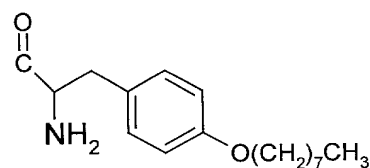
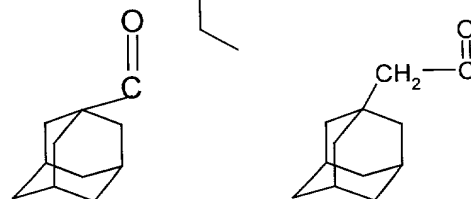
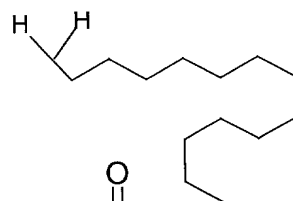


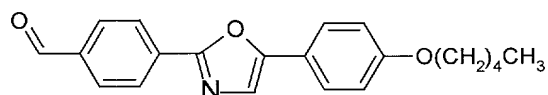
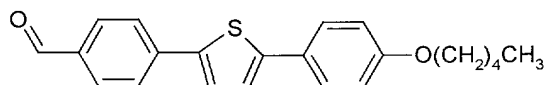
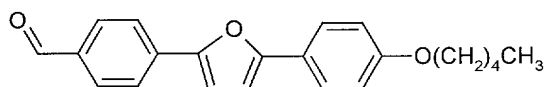
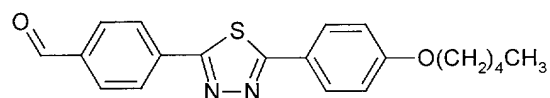
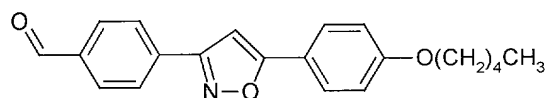
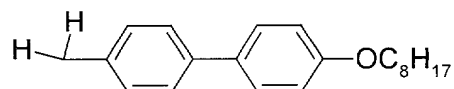
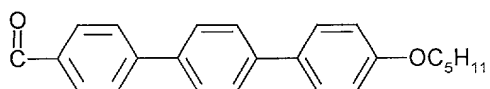
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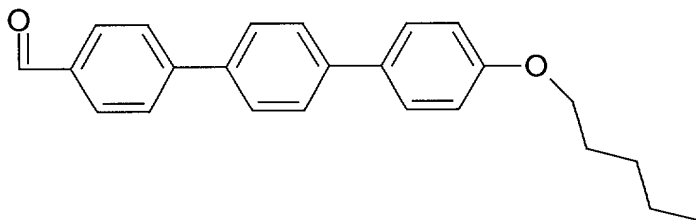




radical.

A most particular subject of the invention is the compounds of formula I in which R represents a

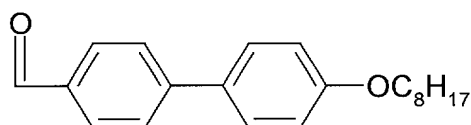
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chain or a

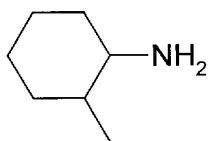
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chain.

Among the preferred compounds of the invention, there can be quite particularly mentioned the compounds of formula I in which R_1 is a hydrogen atom, those in which R_2 is a

20



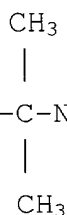
radical,



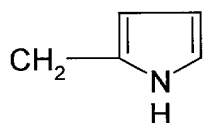
those in which R₂ is a -CH₂-CH-NH₂ radical, a



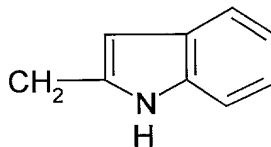
-CH-CH₂NH₂ radical or a CH₂-C-NH₂ radical or also those in



which R₂ is a



or



radical

A most particular subject of the invention is the compounds of formula (I), the preparation of which is given hereafter in the experimental part and in particular the products of Examples 2 and 3.

The compounds of formula (I) have useful antifungal properties; they are in particular active on *Candida albicans* and other *Candida* such as *Candida glabrata*, *krusei*, *tropicalis*, *pseudotropicalis*, *parapsilosis* and *Aspergillus fumigatus*, *Aspergillus flavus*, *Cryptococcus neoformans*.

The compounds of formula (I) can be used as medicaments in man or animals, in particular to combat invasive candidosis in the immunosuppressed, digestive, urinary, vaginal or cutaneous candidosis, cryptococcosis, for example neuromeningeal, pulmonary or cutaneous cryptococcosis, bronchopulmonary and pulmonary aspergillosis and invasive

aspergillosis in the immunosuppressed.

The compounds of the invention can also be used in the prevention of mycotic illnesses in the congenital or acquired immunosuppressed.

- 5 The compounds of the invention are not limited to a pharmaceutical use, they can also be used as fungicides in fields other than the pharmaceutical field.

Therefore a subject of the invention is, as antifungal compounds, the compounds of formula (I) as well as their
10 addition salts with acids.

A subject of the invention is also the compounds of formula (I), as medicaments.

A most particular subject of the invention is the pharmaceutical compositions containing as active ingredient
15 at least one compound of formula (I) or one of its addition salts with pharmaceutically acceptable acids.

These compositions can be administered by oral, rectal, parenteral route or by local route as a topical application on the skin and mucous membranes, but the preferred routes
20 are the oral and parenteral routes.

They can be solid or liquid and can be presented in the pharmaceutical forms commonly used in human medicine, such as for example, plain or sugar-coated tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments,
25 creams, gels; they are prepared according to the usual methods. The active ingredient or ingredients can be incorporated in the excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or
30 non-aqueous vehicles, fatty matter of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

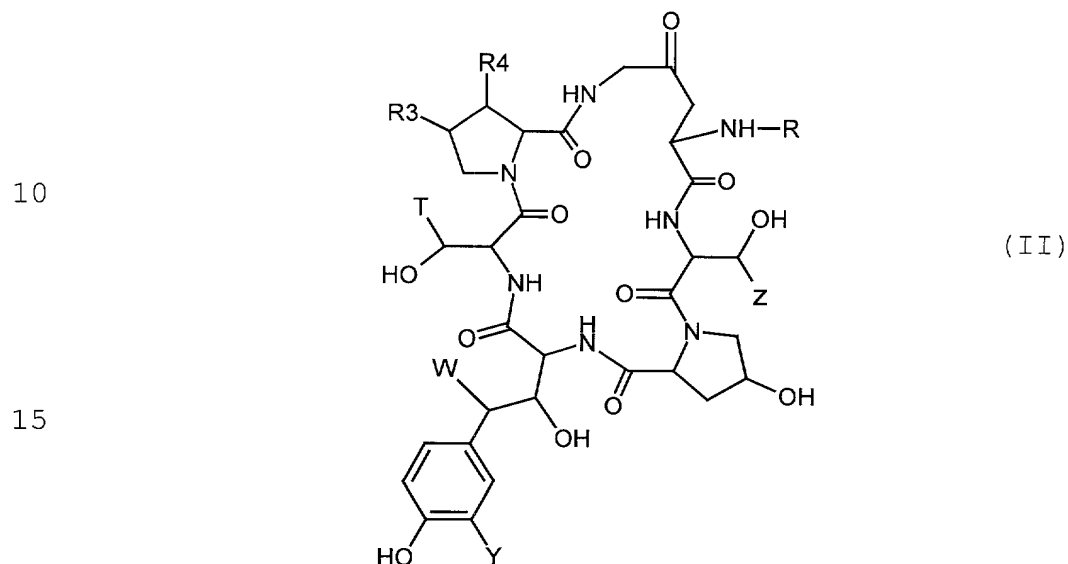
These compositions can also be presented in the form of a powder intended to be dissolved extemporaneously in an
35 appropriate vehicle, for example apyrogenic sterile water.

The dose administered is variable according to the illness treated, the patient in question, the administration route and the product considered. It can be, for example,

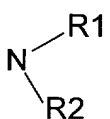
comprised between 50 mg and 1 g per day by oral or parenteral route, in adults for the products of Examples 2 and 3.

A subject of the invention is also a preparation process characterized in that a compound of formula (II)

5



20 in which R, R₃, R₄, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or an amine derivative capable of introducing

25 the  radical in which R₁ and R₂

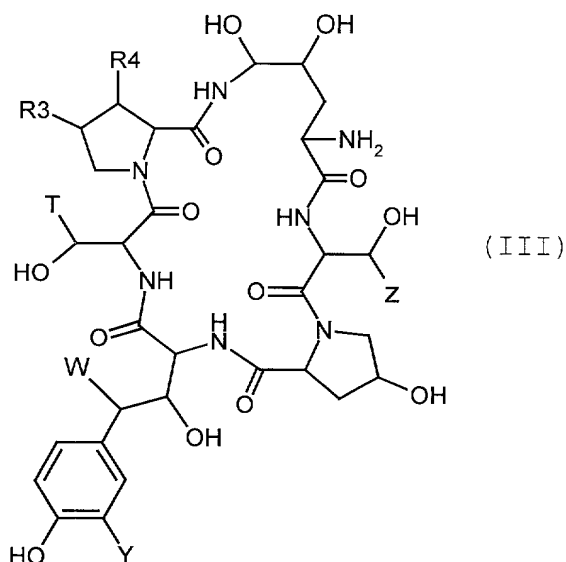
retain their previous meaning and if desired is subjected to the action of a reducing agent and/or of an amine functionalization agent, and/or an acid in order to form the salt of the product

30 obtained,

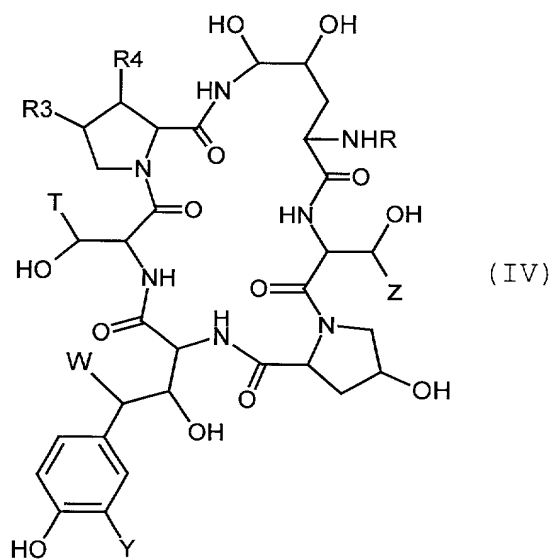
and/or a separation agent of the different isomers obtained, and the sought compound of formula (I) is thus obtained.

The compounds of formula (II) described and claimed in the Patent Application WO 99 29716 can be prepared according

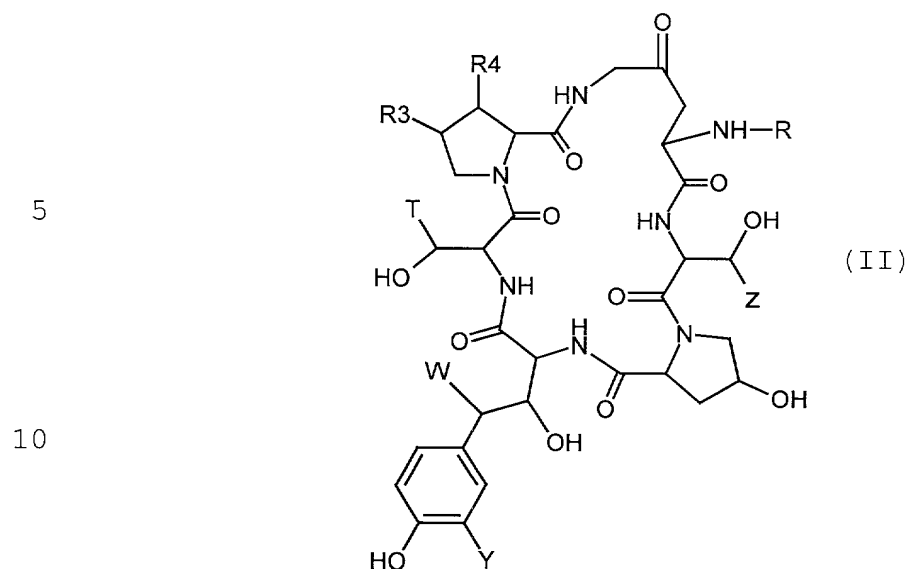
35 to a process characterized in that a compound of formula (III)



15 in which the different substituents retain their previous meaning is subjected to the action of an agent capable of replacing NH_2 with NHR , R retaining its previous meaning in order to obtain the compound of formula (IV)



35 which is subjected to the action of trimethylsilyl iodide in order to obtain the corresponding compound of formula (II)



The following examples illustrate the invention without
15 however limiting it.

Preparation 1: "nucleus" of deoxymulundocandine

2 g of deoxymulundocandine is dissolved in 20 ml of
DMSO. This solution is poured into a suspension containing
120 g of *Actinoplanes utahensis* FH2264 in 870 ml of a KH₂PO₄,
20 K₂HPO₄ buffer (pH: 6.8). The reaction mixture is maintained
under agitation for 70 hours at 30°C. Filtration is carried
out. The mycelium is washed with the phosphate buffer (pH:
6.8). The washing liquids and the filtrate are combined.
The product obtained is chromatographed on a DIAION HP 20
25 resin and a product is obtained which is used as it is
hereafter.

**EXAMPLE 1: 1-[4-[(2S)-2-amino-2-methylethyl)-amino]-N2-[4'-(
(octyloxy) [1,1'-biphenyl]-4-yl)-carbonyl]-L-ornithine]-4-[4-
(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B
30 trifluoroacetate (isomer A and isomer B).**

Stage A: 1-[(4R,5R)-4,5-dihydroxy-N2-[4'-(octyloxy) [1,1'-
biphenyl]-4-yl)-carbonyl]-L-ornithine]-4-[4-(4-hydroxy-
phenyl)-L-threonine]-5-L-serine echinocandine B

1- Preparation of the ester

35 632 mg of 2,3,4,5,6 pentafluorophenol and 695 mg of N,N'-
dicyclohexylcarbodiimide are added to 1 g of 4'-octyloxy-
[1,1'-biphenyl]4-carboxylic acid in 22 ml of tetrahydrofuran,
followed by agitation for 22 hours at ambient temperature and

filtration. The solvents are eliminated under reduced pressure, the residue is taken up in ether, agitated at approximately 35°C, followed by filtration, the solvent is evaporated followed by drying and 1.46 g of expected product is recovered, which is used as it is.

2- Coupling

677 mg of the deoxymulundocandine "nucleus" obtained in Preparation 1 is introduced into 16 ml of DMF. The solution obtained is agitated for 5 minutes and 793 mg of pentafluorophenyl 4'-(octyloxy)-[1,1'-biphenyl]-4-carboxylate obtained above is added. The reaction mixture is maintained under agitation and a nitrogen atmosphere for 24 hours. The reaction mixture is filtered and concentrated. The residue is taken up in ether, triturated, maintained under agitation for 25 minutes, separated, washed with ethyl ether, chromatographed on silica while eluting with a mixture of methylene chloride, methanol, water (86/13/1) then (80/20/1). The sought product is thus obtained. Yield 73%.

Stage B: 1-[N2-[[4'-(octyloxy)-[1,1'-biphenyl]-4-yl]carbonyl]-4-oxo-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B.

311 µl of trimethylsilyl iodide is added to a suspension containing 809 mg of the product of Stage A and 19 ml of acetonitrile. The reaction mixture is maintained under agitation for 15 minutes at 60°C and under a nitrogen atmosphere. The mixture is poured into a saturated solution of sodium thiosulphate followed by evaporation. The residue obtained is chromatographed on silica, eluting with a methylene chloride/methanol/water mixture 86/13/1. The sought product is obtained. Yield 55%.

Stade C: 1-[4-(((2S)-2-amino-2-methylethyl)amino)-N2-[[4'-(octyloxy)[1,1'-biphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer A and isomer B).

A solution containing 62.5 mg of (S)-(-)diaminopropane dihydrochloride, 2.25 ml of methanol, triethylamine in order to obtain a pH of 6, a few grains of activated siliporite and 150 mg of the product of the previous stage is agitated for a

few minutes at 20°C. 6 mg of NaBH₃CN is introduced. Agitation is carried out for 15 hours at 20°C and after semi-preparative HPLC purification (eluent: CH₃CN, H₂O/TFA (50-50-0.02), 11.5 mg of isomer A, 13 mg of isomer B are obtained.

5 **EXAMPLE 2: 1-[4-[(1H-benzimidazol-2-yl)-methyl]-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer B).**

By operating as previously starting from the nucleus of
10 deoxymulundocandine prepared in Preparation 1 and obtaining 1-[(4R,5R)-4,5-dihydroxy-N2-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B as
15 intermediate product and the corresponding 4-oxo derivative, the sought product was obtained. Isomer A = 7.4 mg, isomer B = 1.2 mg.

EXAMPLE 3: Trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

By operating as previously, starting from 166 mg of the 4-oxo derivative prepared above and 78 mg of (1R, 2R)1-2-diaminocyclohexane, 462 mg of crude product is obtained which is chromatographed on silica eluting with a methylene
25 chloride, methanol, H₂O, acetic acid mixture 86/13/2/1. 100 mg of product is obtained which is purified by semi-preparative HPLC again with a CH₃CN/H₂O/TFA mixture = 50/50/0.1. 55 mg of isomer A, 5.2 mg of isomer B are obtained.

30 **EXAMPLE 4: 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).**

By operating as previously, the sought product was
35 obtained.

EXAMPLE: Pharmaceutical composition:

Tablets were prepared containing:

- Product of Example 3 isomer A..... 150 mg

- Excipient s.q.f. 1 g
(Detail of excipient: starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY

5

A - Inhibition of the glucan synthase of *Candida albicans*.

Candida albicans membranes were purified according to the process described by Tang et al Antimicrob. Agents Chemother 35, 99-103, 1991. 22.5 µg of membrane proteins are incubated
10 in a mixture of 2Mm of ¹⁴C-UDP glucose (specific activity = 0.34 mCi./mmol, 50 µg of α-amylase, 1Mm of dithiotreitol (DTT), 1Mm EDTA, 100Mm NaF, 7µM of GTP-γ-S, 1M of sucrose and 50Mm of Tris-HCL (pH 7.8) in a volume of 100µl. The medium is incubated at 25°C for 1 hour and the reaction is
15 terminated by adding TCA at a final concentration of 5%. The reaction mixture is transferred onto a pre-humidified glass fibre filter. The filter is washed, dried and its radioactivity is counted.

Mulundocandine is used as a positive control.

20 Control of the vehicle is carried out with the same quantity of 1% DMSO. The results obtained show that in this test the products of the invention show a good activity in particular the products of Example 3 isomer A.

B - activity on the *Aspergillus fumigatus* enzyme.

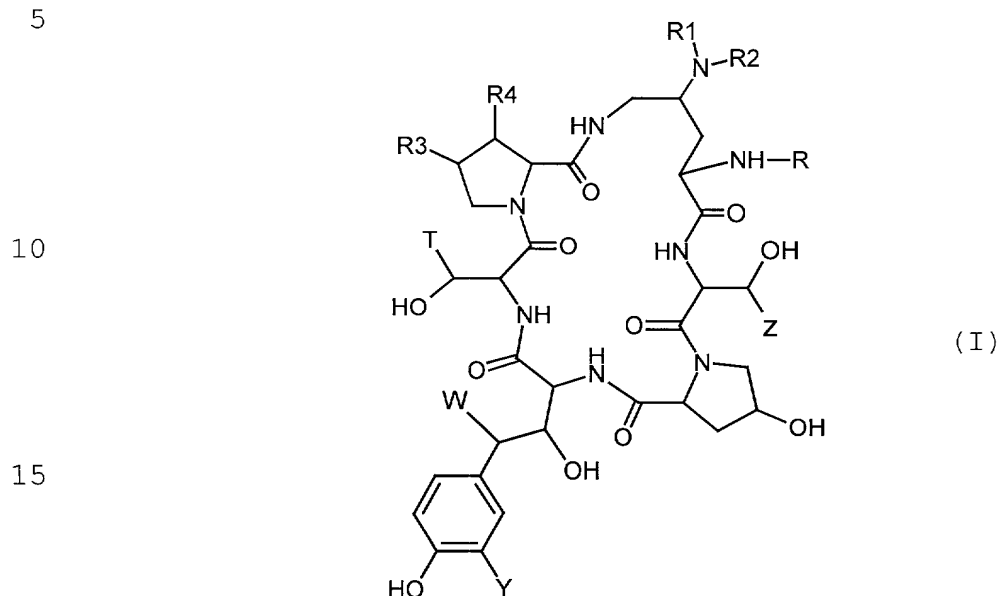
25 The enzyme is prepared according to the process of Beaulieu et al.(Antimicrob. Agents Chenother 38, 937-944, 1994.

The protocol used is identical to the protocol described above for the enzyme of *Candida albicans* except that dithiotreitol is not used in the reaction mixture.

30 In this test the products show a good activity.

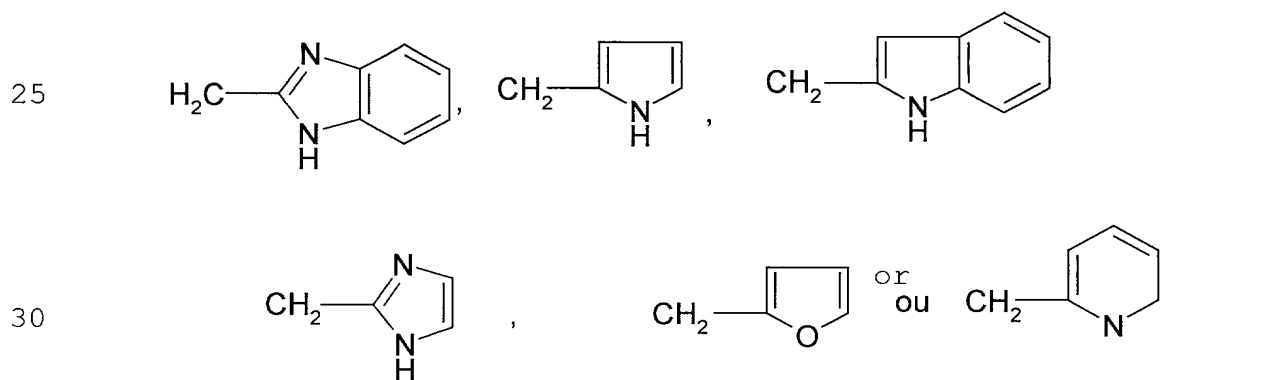
CLAIMS

1) In all possible isomer forms as well as their mixtures, the compounds of formula (I):



in which

20 either R_1 represents a hydrogen atom or a methyl radical.
 R_2 represents a cyclohexyl radical substituted by an amine, a $\text{CH}_2\text{CH}_2\text{NHCH}_3$ radical, a $\text{CH}_2\text{CHCH}_3\text{NH}_2$ radical, a



radical, a $\text{CHCH}_3\text{CH}_2\text{NH}_2$ radical, a $-(\text{CH}_2)_a\text{OH}$ radical, a
 35 representing an integer comprised between 1 and 8, a $(\text{CH}_2)_b\text{-C}\equiv\text{N}$ radical
 b representing an integer comprised between 1 and 8, a
 $\text{CHCH}_3\text{C}_6\text{H}_5$ radical, a $(\text{CH}_2)\text{-C}(\text{CH}_3)_2\text{NHCOCF}_3$ radical, a

CHCH₃(CH₂)_dOH radical, d representing an integer comprised between 1 and 8

or R₁ and R₂ together with the nitrogen which carries them form a ring with 3, 4 or 5 carbons optionally substituted by an amine

R₃ represents a hydrogen atom, a methyl or hydroxyl radical

R₄ represents a hydrogen atom or a hydroxyl radical

R represents a linear or branched or cyclic chain containing up to 30 carbon atoms, optionally containing one or more heteroatoms, one or more heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms optionally containing one or more heteroatoms and/or one or more heterocycles,

T represents a hydrogen atom, a methyl radical, a CH₂CONH₂, CH₂C≡N radical, a (CH₂)₂NH₂ or (CH₂)₂Nalk⁺X⁻ radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO₃H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical,

as well as the addition salts with acids of the products of formula (I).

2) The compounds of formula (I) defined in claim 1 in which T represents a hydrogen atom.

3) The compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.

4) The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

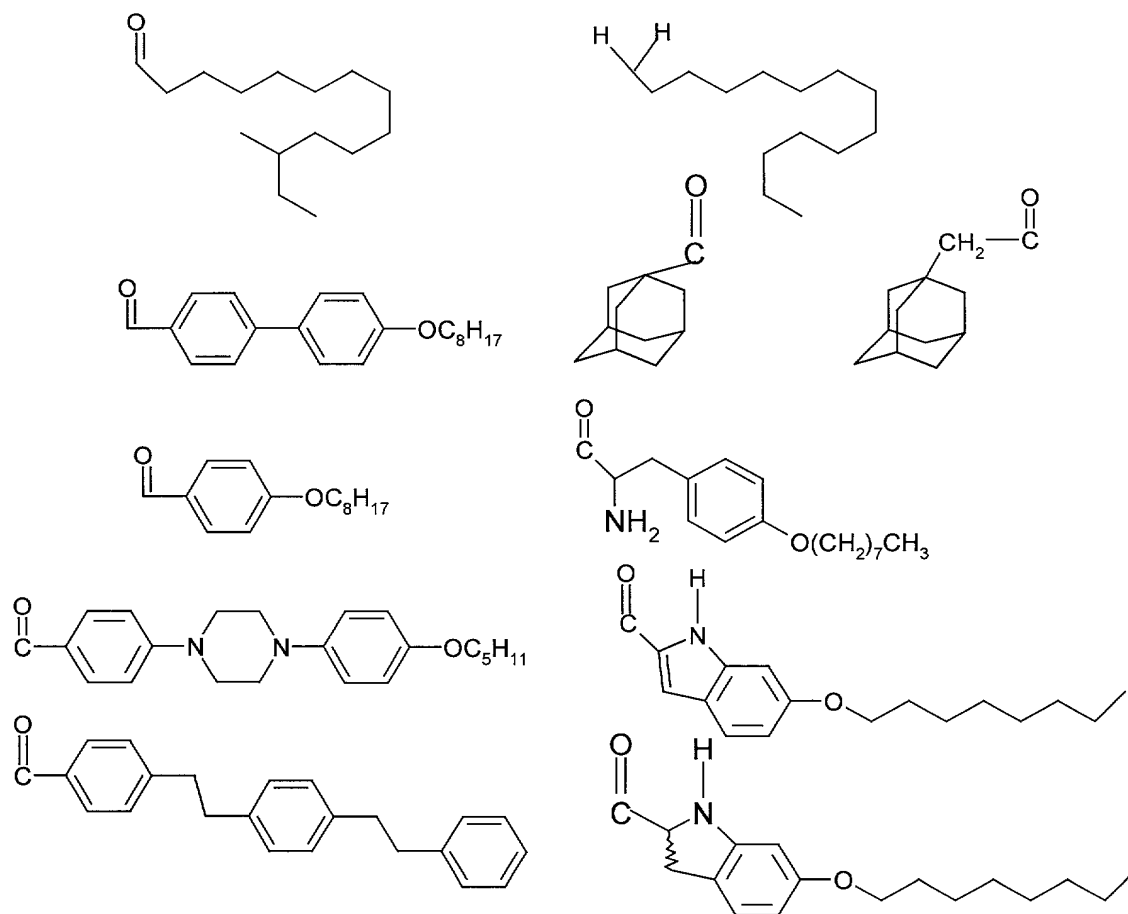
5) The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

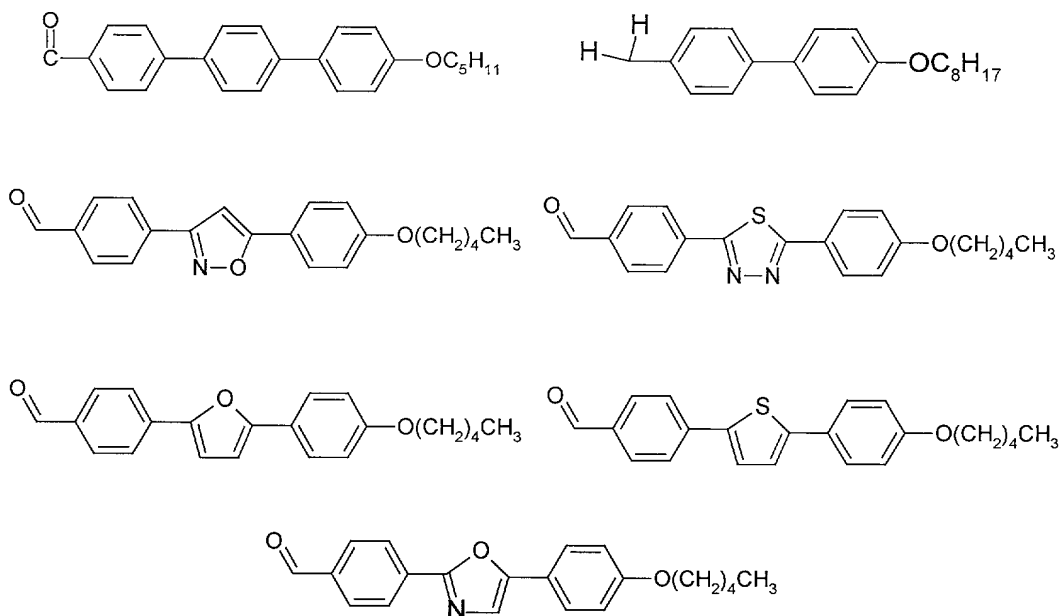
6) The compounds of formula (I) defined in any one of claims 1 to 5 in which R₃ represents a methyl radical.

7) The compounds of formula defined in any one of claims 1 to 6 in which R₄ represents a hydroxyl radical.

8) The compounds of formula (I) defined in any one of claims 1 to 7 in which R represents a

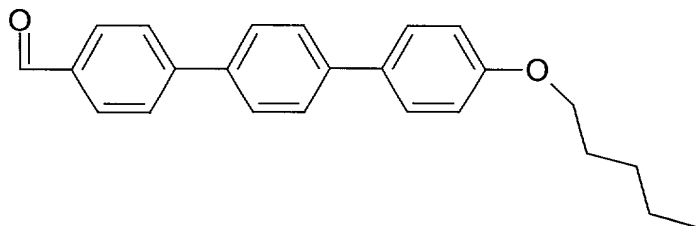
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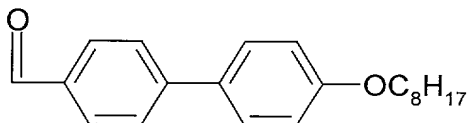
radical.

- 9) The compounds of formula (I) defined in claim 8, in which R represents a



chain.

- 10 10) The compounds of formula (I) defined in claim 8, in which R represents a



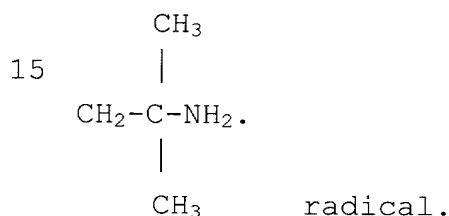
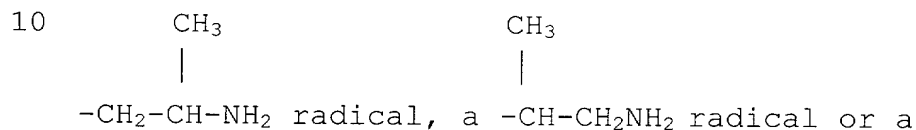
chain.

- 11) The compounds of formula (I) defined in any one of claims 1 to 10 in which R₁ is a hydrogen atom.

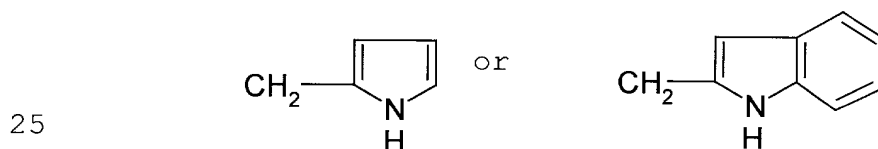
12) The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is a



13) The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is a



14) The compounds of formula (I) defined in any one of claims 1 to 11 in which R₂ is a

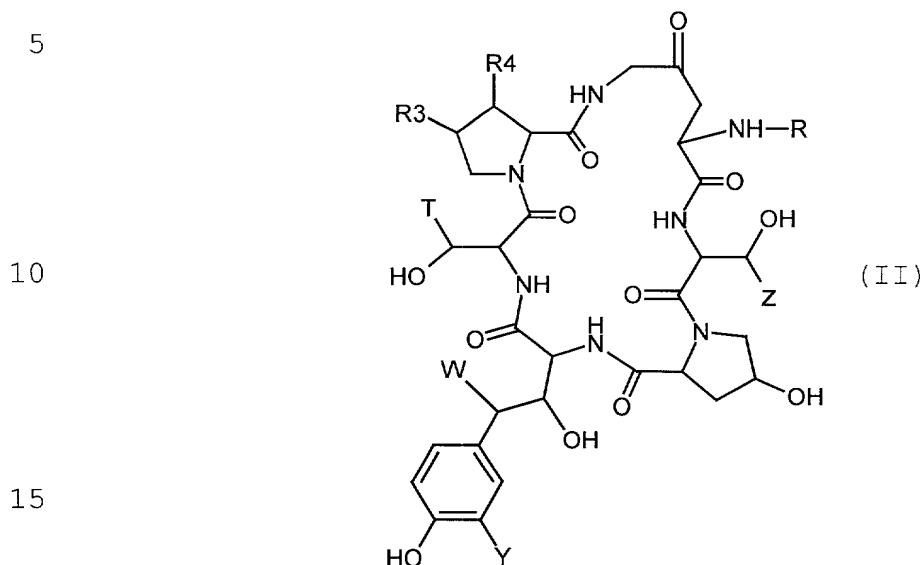


radical.

15) The compounds of formula (I) defined in any one of claims 1 to 14 the names of which follow:

- 30 - 1-[4-[[[1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B),
- 35 - trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4''-(pentyloxy)[1,1':4',1''-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

16) Process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15 characterized in that a compound of formula (II)



in which R, R₃, R₄, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or amine derivative capable of introducing

the $\begin{array}{c} \text{R}_1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}_2 \end{array}$ radical in which R₁ and R₂

25 retain their previous meaning and if desired to the action of a reducing agent and/or an amine functionalization agent, and/or an acid in order to form the salt of the product obtained,

30 and/or a separation agent of the different isomers obtained, and the sought compound of formula (I) is thus obtained.

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

35 **18)** The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.

**DECLARATION FOR
UTILITY OR DESIGN
PATENT APPLICATION**☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket Number	146.1374
First Named Inventor	J.L. LALANNE et al
COMPLETE IF KNOWN	
Application Number	PCT/FR00/01567
Filing Date	June 8, 2000
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**NOVEL CANDIDA ALBICANS GENES AND PROTEINS
CODED BY THESE GENES**

(Title of the Invention)

the specification of which

☐ is attached hereto
OR☒ was filed on (MM/DD/YYYY)

June 9, 2000

as United States Application Number or PCT International

Application Number

PCT/FR00/01567

and was amended on (MM/DD/YYYY)

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
99/07250	France	6/9/99	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

(Page 1 of 5)

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(January 1997)

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian	19,683		
Jordan B. Bierman	18,629		
Donald C. Lucas	31,275		
Bierman, Muserlian and Lucas	18,818		

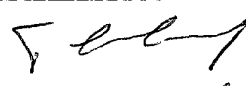
☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	Bierman, Muserlian and Lucas		
Address			
Address	600 Third Avenue		
City	New York	State	New York
Country	U.S.A.	ZIP	10016
Telephone	(212) 661-8000	Fax	(212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and (further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon)

Name of Sole or First Inventor:		<input type="checkbox"/> A petition has been filed for this unsigned inventor	
Given Name	JEAN	Middle Initial	L
Family Name	LALANNE	Suffix e.g. Jr.	

Inventor's Signature		Date	December 17 th 2001
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Residence: City	Fontenay sous Bois	State		Country	France	Citizenship	FR
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Post Office Address	
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Post Office Address	110. avenue du Marechal
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City	Fontenay sous Bois	State		Zip	F-94120	Country	France
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☒ Additional inventors are being named on supplemental sheet(s) attached hereto



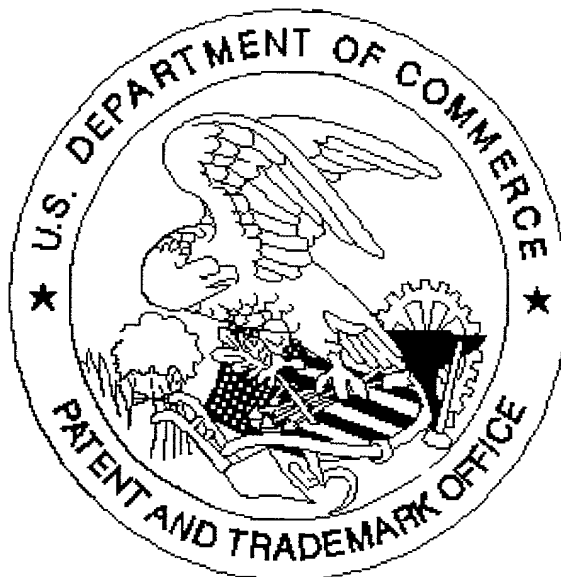
DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name	CORINNE	Middle Initial		Family Name	ROCHER	Suffix	e.g. Jr.
Inventor's Signature					Date	December 13, 2001	
Residence: City	Paris	State		Country	France	Citizenship	FR
Post Office Address							
Post Office Address		3, rue Elisa Lemonnier					
City	Paris	State		Zip	F-75012	Country	France
Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name		Middle Initial		Family Name		Suffix	e.g. Jr.
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	
Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name		Middle Initial		Family Name		Suffix	e.g. Jr.
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
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Post Office Address							
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Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name		Middle Initial		Family Name		Suffix	e.g. Jr.
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	
Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name		Middle Initial		Family Name		Suffix	e.g. Jr.
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
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Post Office Address							
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